PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference	**FOR FURTHER ACTION**
see form PCT/ISA/220	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/052389	30.09.2004	01.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07D211/42, C07D413/12, C07D401/12, A61K31/395

Applicant
SPEEDEL EXPERIMENTA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/052389

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9

because:

☒ the said international application, or the said claims Nos. 9 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4
	No:	Claims	1-3,5-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-8,10
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 97/09311 A1 (F. HOFFMANN-LA ROCHE AG, SWITZ.)
D2: GULLER, ROLF ET AL: "Piperidine-renin inhibitors compounds with improved physicochemical properties" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 9(10), 1403-1408 CODEN: BMCLE8; ISSN: 0960-894X, 1999
D3: MARKI, H. P. ET AL: "Piperidine renin inhibitors: from leads to drug candidates" FARMACO , 56(1-2), 21-27 CODEN: FRMCE8; ISSN: 0014-827X, 2001
D4: HELMESTE, D.M.; ET AL.: EUSOPEAN JOURNAL OF PHARMACOLOGY, vol. 288, 1995, pages 373-377
D5: WO 00/64887 A (F. HOFFMANN-LA ROCHE AG)
D6: WO 2004/002466 A (SPEEDEL PHARMA AG; RIEDL, JUTTA; KANNAH, SATISH; DIETERLE, WALTER)
D7: WO 2004/089903 A (WARNER-LAMBERT COMPANY LLC; CODY, WAYNE, LIVINGSTON; EDMUNDS, JEREMY,)

item **III**

For the assessment of the present claim 9 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

item **V**

1. Novelty (Art. 33(2) PCT)

1.1. Document D3 discloses compounds which appear to be falling within the scope of present claims 1-3 and 5 (see table 2 on p. 29, compounds 26-36). D4 discloses the

compound paroxetine, which appeas to be falling within the scope of present claims 1-3, 6 and 7 (col. 2). Document D5 discloses compounds of general formua I which appears to overlap with the subject-matter of present claims 1-3 and 5-7 (see also the examples of D5). All of the cited compounds would appear to fall within compound (I) of the present application wherein R^1 has the meaning (B). The cited documents are also considered as to disclose the subject-matter of present claims 8-10.

The application therefor doesn't meet the requirements of Art. 33(2) PCT.

1.2. The subject-matter of present claim 4 is considered novel.

2. Inventive step (Art. 33(3) PCT)

2.1. The present application relates to renin inhibitors on the basis of substituted piperidines. Document D1 discloses these compounds of general formula (I), wherein the substituent R^1 is defined as Aryl or Heterocyclyl, and their use as renin inhibitors. Claim 1 of the present application defines that substituent as either being selected from particular cyclic moieties (A) or as aryl or heterocyclyl being substituted by a variety of groups ((B) to (F)). All of the substituents R^1 according to the present application are considered as to fall within the definition "Aryl or Heterocyclyl" according to D1, in particular since these groups can optionally be substituted (p. 7, l. 12 ff). It would thus appear that the skilled person can, in order to solve the technical problem of providing, starting from D1, further compounds as renin inhibitors, be expected to provide compounds of general formula (I) according to present claim 1. Since the application documents presently on file do not appear to contain data showing a particular effect of the claimed compounds when compared to the compounds disclosed in D1, the objective problem can indeed only be seen in the provision of alternative compounds. This, however, cannot be considered based on an inventive step with respect to D1. Since none of the dependent claims nor independent claims 8-10 appear to contain additional subject-matter which can be taken as a basis for acknowledging the presence of an inventive step, the application does not meet the requirements of Art. 33(3) PCT.

2.2. It is noted that the examples are much narrower in scope than the definition of the compounds according to the present claims, i.e. Q is always absent, R^3 and R^4 are H,

W is absent (m = 0), X is oxygen and R^2 is always p-substituted phenyl. Although a generalisation of the examples is acceptable, the broad scope is at the present stage not acceptable. It is to be noted that an alleged technical effect should be made credible for essentially all of the claimed subject-matter. Even if applicant can show that the examples exhibit properties which can be seen unexpected with respect to D1, the claimed scope should be limited to compounds for which such an effect can be shown.

2.3. Applicant is also informed that the presently claimed subject-matter would appear to be non-unitary as long as no special technical feature can be identified. Since some of the compounds are known in the same technical field (see novelty) and alternative compounds are known from D1, the claimed compounds do not contain a common structural feature which is not known (the common feature is either a linear substituent (B) or a cyclic substituent (C) which is attached to an aryl or heterocyclyl group, or it is a heterocyclic group as such (A); all these features, however, are known). In case applicant cannot identify a special technical feature combining all of the claimed compounds, he should be prepared to face a non-unity objection in a later stage of the proceedings.

3. Industrial applicability (Art. 33(4) PCT)

Can be acknowledged for claims 1-8 and 10.

item **VI**

Document D6 was published after the priority date of the present application but before its international filing date. Its content would be considered as forming part of the state of the art if the priority of the present application was found to be invalid. Documents D6 and D7 will be considered for the question of novelty in the regional european phase even in case the claimed priority is valid.

item **VII**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2-D6 is not mentioned in the description, nor are these documents identified therein.